Internship Proposition
(one page max)
Master 2 GP Immunology & ImmunoIntervention (I^3)
2024-2025

Lab: Nucleotide excision repair and cancer

Team: H. Wurtele and E. Drobetsky

Name and position of the supervisor: H. Wurtele and E. Drobetsky

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Candidate (if internship filled):

Title of the internship: Modulation of nucleotide excision repair by cyclin D1 overexpression in skin cancer

Summary of the internship proposal:

Nucleotide excision repair (NER) is the primary pathway in humans for removing solar UV-induced DNA photoproducts that can lead to malignant melanoma (MM). We used a genome-wide loss-of-function screen to find genes needed for efficient NER in primary human fibroblasts (PMID: 37301510). This screen showed that Dyrk1A promotes NER specifically during the S phase of the cell cycle. Dyrk1A is a dual specificity kinase that phosphorylates cyclin D1 on threonine 286 (T286), causing its relocation to the cytoplasm and degradation, which is essential for the G1-S phase transition and cellular proliferation regulation. Cyclin D1 is often overexpressed in various cancers, including MM. In UV-irradiated HeLa cells, depleting Dyrk1A leads to overexpression of cyclin D1, which inhibits NER during S phase and reduces cell survival. Our data suggest that inhibiting NER during S phase might be a new non-canonical mechanism by which oncogenic cyclin D1 contributes to MM development, though the molecular basis is unknown.
To address this, we propose three aims:
1. Evaluate if NER protein expression and/or recruitment to damaged DNA is defective post-UV in cyclin D1-overexpressing cells during S phase.
2. Identify cellular pathways involved in NER abrogation in cells overexpressing cyclin D1, hypothesizing that overexpression alters protein interactions and/or transcriptional patterns negatively affecting NER during S.
3. Determine the impact of cyclin D1 overexpression on NER and mutagenesis in a panel of MM cell lines.
Perspectives: NER is a critical defense against melanomagenesis. This research aims to clarify how oncogenic cyclin D1 impairs NER, with significant implications for MM and potentially other major cancers. Techniques to be used in the internship include molecular biology, cell biology (flow cytometry/microscopy), bioinformatics, and biochemistry.

Option(s) linked to the project:

☐ Clinical Research Profile (Recherche Clinique)
☐ Data Analyst Profile (Recherche et Analyse de Données Biologiques)
x Experimental Biology Profile (Recherche Expérimentale)

Form to be sent by email to : gpi3@univ-nantes.fr